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510(k) SUMMARY FOR THE ONCOGENE SCIENCE/Bayer Diagnostics Complexed Prostate Specific Antigen (cPSA) Microtiter ELISA

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K002313

1. Submitter Information

Prepared 8/22/00

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2. Device Information

Trade Name:	Complexed PSA Microtiter ELISA
Common Name:	Complexed PSA Immunoassay
Classification Name:	Tumor-Associated Antigen Immunological Test Systems Reclassified to Class II effective 9/19/96

3. Predicate Device Information

Name:	Bayer Immuno 1™ System Complexed PSA Assay
Manufacturer:	Bayer Corporation
510(k) Number:	K980376

4. DEVICE DESCRIPTION

In prostate cancer patients, serum levels of Prostate Specific Antigen (PSA) have been shown to increase or decrease with changes in disease burden. PSA is a serine protease that has been found to exist in serum in free form and bound to various protease inhibitors. The bound forms of PSA include complexes with α-2-macroglobulin, α-1-antichymotrypsin (ACT) and small amounts of α-1-antitrypsin and inter-α-trypsin inhibitor. α-2-macroglobulin surrounds PSA rendering it unmeasureable by immunological techniques. However, complexes of PSA with ACT are readily measurable in serum and constitute the largest proportion of immunoreactive Total PSA in serum. In addition, the proportion of PSA complexed with α-1-antichymotrypsin is increased in the serum of men with prostate cancer (CaP) as compared with healthy men or men with BPH. Accurate longitudinal measurements of serum Complexed PSA (cPSA) during the course of disease and therapy can be used as an adjunctive test in the management of prostate cancer patients. Increases in human serum levels of cPSA are observed in prostate cancer, benign prostatic hypertrophy or inflammation of the genitourinary tissues. cPSA concentrations are not elevated in serum from patients with cancers of the breast, lung, colon, rectum, stomach, pancreas or thyroid. Longitudinal measurements of serum cPSA are valuable for monitoring prostate cancer patients since detectable levels of cPSA following radical prostatectomy can indicate disease recurrence while low cPSA levels indicate disease-free intervals.

In this 510(k) premarket notification, the performance and clinical safety and effectiveness of the Oncogene Science **Complexed Prostate Specific Antigen Microtiter ELISA** has been established by comparison to a predicate device, the Bayer Immuno 1™ Complexed PSA Assay, in accordance with the "Guidance Document For Submission of Tumor Associated Antigen Premarket Notifications, 510(k), to the FDA". In this submission the assay is also referred to as the Complexed PSA Manual ELISA. Non-clinical studies indicate this assay is a stable, reproducible, highly specific and sensitive assay in which serum components and therapeutic agents do not interfere.

Clinical studies indicate substantial equivalence to the predicate device in patient populations. During this study, Oncogene Science Diagnostics, Inc. was purchased by Bayer Corporation.

The Complexed Prostate Specific Antigen Manual ELISA is a sandwich enzyme immunoassay which utilizes a mouse monoclonal antibody (MM1) for capture and an alkaline phosphatase labeled polyclonal anti-PSA antibody (MP-2) for detection. The assay also uses a third antibody that specifically binds free PSA, but not cPSA, thereby allowing the assay to specifically measure cPSA in the presence of Free PSA. All three antibodies specifically bind human PSA, are supplied by our manufacturing site, Bayer Corporation, in Elkhart, Indiana and are the same antibodies used in the predicate device for this study – Bayer Immuno 1™ Complexed PSA assay. The capture antibody has been immobilized on the interior surface of the microtiter plate wells. To perform the assay, an appropriate amount of serum is diluted in sample diluent containing a second anti-PSA antibody designated ME-2. The ME-2 antibody specifically binds to Free PSA (not to cPSA). Thus, the Free PSA is rendered unavailable for binding the detector antibody. After the appropriate incubation period, the captured cPSA is reacted with a polyclonal antiserum conjugated to alkaline phosphatase. The amount of detector antibody bound to cPSA is measured with Blue Phos™ substrate catalyzed to produce a colored product, allowing quantitation by spectrophotometry. Six prepared cPSA standards around 0, 0.5, 1, 5, 10 and 25 ng/ml allow construction of a standard curve for subsequent quantification of Complexed PSA in serum samples. Each kit includes a product insert showing exact concentrations for each lot of Complexed PSA standards. Oncogene Science Complexed PSA ELISA Controls (Product #22-CVX) were assayed in each run for quality control of assay performance. These controls have been developed by Oncogene Science and are sold as a separate product from the kit. Section 9 of this submission provides information and Appendix A5 provides data on these controls, for which we are also seeking approval to market.

5. STATEMENT OF INTENDED USE

The Oncogene Science **Complexed Prostate Specific Antigen Microtiter ELISA** is an *in vitro* diagnostic assay intended to quantitatively measure Complexed PSA in human serum. These cPSA values should be used in conjunction with information available from clinical and other diagnostic procedures as an aid in the management of prostate cancer patients.

6. SUMMARY OF STUDIES

Nonclinical performance characteristics of the **Complexed Prostate Specific Antigen Microtiter ELISA** were determined at Oncogene Science. These studies included tests for parallelism, linearity, cross-reactivity, interfering compounds, heterophile and human anti-mouse antibody and rheumatoid factor interference, stability and sterility.

The clinical study was retrospective, using banked serum samples obtained by DOCRO, Inc. from institutional specimen banks. The study was separated into 3 parts, with all samples analyzed in the ELISA at DOCRO, Inc. and all samples analyzed in the predicate device at Oncogene Science. Data was supplied to DOCRO to perform the statistical analysis.

Part I looked at a monitoring cohort with 4-6 serial serum specimens from 60 patients with prostate carcinoma, obtained from two clinical institutions. Both assay results are compared graphically for progressing, responding and stable patients.

Part II was a Clinical Method Comparison statistically analyzing results from both devices for 200 Normal healthy men and for 300 men with prostate diseases. Cumulative frequency distributions and 90 and 95^{th} order statistics are compared in the normal cohort. Regression analyses determine the functional relationship between the test device and the predicate device for various prostate disease groups. Substantive Equivalence among patient groups for the two devices is shown with mean comparisons.

Finally, Part III determined assay variability and analytical sensitivity by analyzing intra-assay, inter-assay and inter-laboratory variability of three quality control materials, three test control materials and six standards in a 20 day Precision study (NCCLS EP5-T2) performed at three laboratory sites.

7. PERFORMANCE DATA – NONCLINICAL STUDIES

7.1 Antibody and Antigen Characterization.

The capture antibody (anti-PSA mouse monoclonal), the detector antibody (anti-PSA polyclonal) and a third antibody (anti-free PSA mouse monoclonal) used in the Sample Reaction Buffer are all supplied by our manufacturing site, Bayer Diagnostics in Elkhardt, Indiana after purification and characterization including electrophoretic mobility, antibody PI and protein content. The Oncogence Science Complexed PSA ELISA standards are PSA/ACT complex from Scripps Laboratories, San Diego, CA, CAT# P0624. This cPSA standard antigen was characterized by non-reducing SDS PAGE and results are consistent with literature references.

7.2 Parallelism, Linearity, and Spike and Recovery

When serum samples are serially diluted in Sample Diluent (or diluted to 75%, 50%, 25% and 10% in sample diluent), 87-111% recovery is obtained, validating the Sample Diluent as appropriate for diluting and measuring human serum for cPSA. Linearity of the assay was indicated by dilution of patient serum samples with a male serum pool at equally spaced proportions of sample concentration and gave percent recoveries from 95-112%. Analyte spiked into 3 patient sera at 3 spike levels gave average percent recoveries of expected values (versus sample diluent spiked with analyte) of 101%. Therefore serum sample matrix does not affect the ability of the Oncogene Science Complexed PSA ELISA to accurately measure Complexed PSA in serum.

7.3 Cross Reactivity and Interference Testing

Three protease inhibitors, Kallikrein, Trypsin and Chymotrypsin, are in the same family as PSA and show high homology with PSA. When each was spiked into two male serum pools at 5 final concentrations (higher than normally present in patient sera), there was no effect on the recovery of cPSA from these samples, suggesting that none of these proteins cross-react in the assay.

cPSA measurements might be performed while patients are taking vitamins, over-the-counter drugs, or undergoing chemotherapy, therefore, these potential exogenous interferents were spiked into a positive control serum pool which was then analyzed for cPSA. Potential endogenous interferents found as common serum components were analyzed similarly. All compounds tested allowed close to 100 % recovery of Complexed PSA, suggesting that none of these materials interfered with measurement of cPSA.

The potential non-specific reactivity of HAMA (human anti-mouse antibodies) and of rheumatoid factor in the ELISA were investigated. The Oncogene Science Complexed PSA assay uses one mouse monoclonal antibody for capture, a goat polyclonal antibody for detection, and another mouse monoclonal antibody in the sample reaction buffer. To reduce the interference from heterophile antibodies, mouse IgG is incorporated into the sample diluent. Testing a number of HAMA and rheumatoid factor positive serum samples indicated there is no significant interference from such samples in the Oncogene Science Complexed PSA ELISA.

7.4 High-Dose Hook Effect and End-to-End Variation

A 100 µg/ml stock solution of PSA-ACT was diluted 6 times and assayed to show that no high-dose hook effect is observed in the ELISA when samples containing very high levels of Complexed PSA are assayed in the microtiter ELISA.

For end-to-end variation analysis, timing of critical procedural steps was altered from sample to sample within a single run. These experiments showed that greatly

extended incubation times could result in erroneously increased or decreased recoveries of Complexed PSA (up to 19%). However, during normal use following instructions, expected variance in timing of each of the reagent steps is expected to fall well short of these extended times.

7.5 Plate Coating Variability and Device Stability

When a Serum sample pool was assayed over an entire plate, a coefficient of variance of 7.7% was observed indicating consistent sample recovery. Thus uniform antibody coating is indicated throughout the plate. Complexed PSA standards exhibit long term stability (>18 months). Performance of Complexed PSA ELISA kits remains robust and consistent when stored for at least 8-9 months post-manufacture at the recommended storage temperature.

7.6 Reagent Bioburden and Preservative Effectiveness Evaluation

Multiple aliquots of the liquid components of the Oncogene Science Complexed PSA ELISA (all greater than 8 months post-manufacture) were tested at Mycoscience, Inc. No reagent was capable of maintaining or promoting growth of aerobic bacteria, yeast or mold.

7.7 Sample Handling

cPSA recovery was analyzed after storage of patient serum samples or Oncogene Science PSA-ACT Controls at 4°C and -20°C for 32 days, as well as after multiple freeze/thaw cycles prior to assay. cPSA is stable in human serum for all of these conditions, including after at least 6 cycles of freezing and thawing.

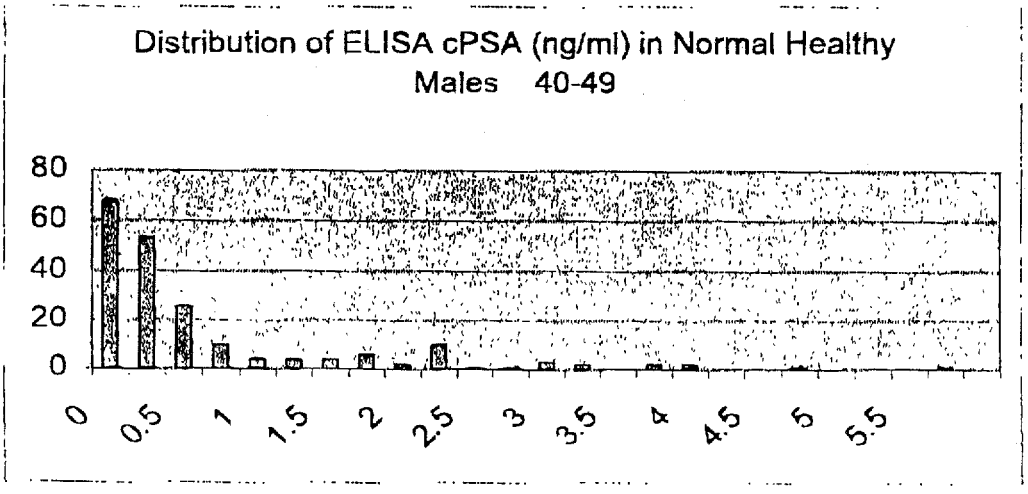
8. PERFORMANCE DATA – CLINICAL STUDIES

Part I – Monitoring. In 58/60 patients, test and predicate device longitudinal graphs are close to or completely superimposable. In one case, both devices give very

high cPSA values but the predicate device plateaus out at a high 500 ng/ml, while the ELISA continues to increase. In another case, the trends are somewhat different between the predicate and test device graphs, but both devices give very high cPSA values. In 59 cases, the two devices show the same trend, indicating substantial equivalence of the ELISA to the predicate device as an aid in the management (monitoring) of prostate cancer patients. Further, in most cases there is a direct relationship between changes in Complexed PSA concentration and clinical course of disease, demonstrating the clinical utility of this assay, when used in conjunction with other clinical indicators, to confirm response to therapy and to signal possible recurrence of malignant disease.

Part II – Clinical Method Comparison.

A) Cutoff - The cumulative distributions of a normal healthy cohort of 200 men ages 40-49 were similar between the predicate and test devices. Analysis of a revised cohort (seven outliers removed) shows that the 95th order statistic for the predicate device, Immuno 1^{TM}, is 2.98 ng/ml cPSA (95% confidence interval:2.58-3.51), while for the ELISA it is 2.37 ng/ml cPSA (95% CI:2.13-3.04). A Demmings Method Comparison of results from the two assays gives a Slope of 1.01 (Identity Line = 1.0) for all 200 men and 0.82 for the revised cohort. The predicate and test devices give comparable results on the Normal Patients. The Distribution of cPSA is shown in the chart below.



B) Method Comparison – Regression analysis on a prostate disease cohort of 293 men was used to determine the functional relationship between the test and predicate devices. Based on biopsy results, this group consisted of 29% normal, 18 % BPH, 12 % prostatitis, 5 % PIN/Suspicious and 35 % prostate cancer. Mean Complexed PSA values were similar in each group except the malignant group, which had higher values. There were statistically significant differences in cPSA values between the predicate and test devices in all biopsy groups by Greenhouse-ANOVA, however these differences ranged from 0.17 ng/ml (PIN) to 0.7 ng/ml (malignant) and are within the CV of the test device at those mean values. A Demings method for each subgroup of the prostate disease cohort shows agreement between the values of the predicate and test devices of:

Test device = 0.924 * (predicate device) – 0.232	N=85	Normal Biopsy
Test device = 0.998 * (predicate device) – 0.463	N=53	BPH
Test device = 1.079 * (predicate device) – 0.81	N=51	Prostatis/PIN/Susp
Test device = 1.002 * (predicate device) – 0.72	N=104	Malignant

This indicates a proportional and constant bias in two sub-cohorts of 7-8% of the predicate device value, within the % CV of the test assay. Two sub-cohorts have no proportional bias. Therefore, these two devices are substantially equivalent for analysis of men with prostate disease.

Finally, for the combined study, 486 samples of both normal and prostate disease patients, in the range of 0 to 76.2 ng/ml, the relationship between the Complexed PSA Microtiter ELISA and the predicate device is described by the equation:

ELISA cPSA = 0.9886(predicate device) – 0.395

Correlation coefficient (r) = 0.98

Expected ELISA Values for Complexed PSA in Normals and in Disease Groups

	N	% Distribution of cPSA by Disease Category				
		0-3.75 ng/ml	3.76-10.0 ng/ml	10.1-30.0 ng/ml	30.1+ ng/ml	Mean (ng/ml)
Healthy Normals	193	98.5	2.5	0	0	0.67
Biopsy Results	293					
Normal Biopsy	85	38.8	55.3	5.9	0	4.72
BPH	53	41.5	50.9	7.6	0	5.07
Prostatitis	36	50.0	44.4	2.8	2.8	5.92
PIN/Suspicious	15	40.0	60.0	0	0	4.20
Prostate Cancer	104	26.9	51.9	17.3	3.9	8.12
by Gleason						
3	1	100.0				
4	6	33.3	66.7			
5	11	27.3	54.5	18.2		
6	56	32.1	57.1	8.9	1.8	
7	18	22.2	27.8	44.4	5.6	
8	10		60.0	30.0	10.0	
9	2		50.0		50.0	

9. CONCLUSIONS

9.1 Device Performance

The Oncogene Science Complexed PSA Microtiter ELISA is reproducible, shows good linearity and parallelism, and has no cross-reactivity, high-dose hook effect, or interference problems.

9.2 Substantial Equivalence

Comparison of clinical sample results from the Oncogene Science Complexed PSA Microtiter ELISA and from the Bayer Immuno 1™ Complexed PSA, for which there is an approved 510(k), demonstrate that the two devices are equivalent with respect to method performance, clinical utility and device safety and effectiveness. The two devices give equivalent results in analysis of men with benign prostate disease and in men with prostate cancer. Longitudinal measurements of cPSA using both assays for monitoring men with prostate cancer gave superimposable results graphically.

DEPARTMENT OF HEALTH & HUMAN SERVICES

AUG 3 0 2000

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Ms. Sheryl Brown-Shimer
Manager, Clinical Trials
Oncogene Science
Bayer Corporation
80 Rogers Street
Cambridge, Massachusetts 02142-1168

Re: K002313
Trade Name: Oncogene Science Complexed PSA Microtiter ELISA
Regulatory Class: II
Product Code: LTJ
Dated: July 28, 2000
Received: July 31, 2000

Dear Ms. Brown-Shimer:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510 (k) Number (if known): K002313

Device Name: Oncogene Science Complexed PSA Microtiter ELISA

Indications For Use:

The Oncogene Science Complexed Prostate Specific Antigen (cPSA) Microtiter ELISA is an *in vitro* diagnostic assay intended to quantitatively measure Complexed PSA in human serum. These Complexed PSA values should be used in conjunction with information available from clinical and other diagnostic procedures as an aid in the management of prostate cancer patients.

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Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ OR Over-the-counter Use _____
(per 21 CFR 801.109)

(Optional Format 1-2-96)

Peter E. Maker
(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K002313